

# Brain Changes Induced by Electroconvulsive Therapy Are Broadly Distributed

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## ABSTRACT

**BACKGROUND:** Electroconvulsive therapy (ECT) is associated with volumetric enlargements of corticolimbic brain regions. However, the pattern of whole-brain structural alterations following ECT remains unresolved. Here, we examined the longitudinal effects of ECT on global and local variations in gray matter, white matter, and ventricle volumes in patients with major depressive disorder as well as predictors of ECT-related clinical response.

**METHODS:** Longitudinal magnetic resonance imaging and clinical data from the Global ECT-MRI Research Collaboration (GEMRIC) were used to investigate changes in white matter, gray matter, and ventricle volumes before and after ECT in 328 patients experiencing a major depressive episode. In addition, 95 nondepressed control subjects were scanned twice. We performed a mega-analysis of single subject data from 14 independent GEMRIC sites.

**RESULTS:** Volumetric increases occurred in 79 of 84 gray matter regions of interest. In total, the cortical volume increased by mean  $\pm$  SD of  $1.04 \pm 1.03\%$  (Cohen's  $d = 1.01$ ,  $p < .001$ ) and the subcortical gray matter volume increased by  $1.47 \pm 1.05\%$  ( $d = 1.40$ ,  $p < .001$ ) in patients. The subcortical gray matter increase was negatively associated with total ventricle volume (Spearman's rank correlation  $\rho = -.44$ ,  $p < .001$ ), while total white matter volume remained unchanged ( $d = -0.05$ ,  $p = .41$ ). The changes were modulated by number of ECTs and mode of electrode placements. However, the gray matter volumetric enlargements were not associated with clinical outcome.

**CONCLUSIONS:** The findings suggest that ECT induces gray matter volumetric increases that are broadly distributed. However, gross volumetric increases of specific anatomically defined regions may not serve as feasible biomarkers of clinical response.

**Keywords:** Antidepressant, Biomarker, Brain, Depression, ECT, Magnetic resonance imaging, Neuroimaging

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Depressive disorders are now the leading cause of years lived with disability worldwide (1), with an estimated 300 million people being affected (2). Electroconvulsive therapy (ECT) remains the most efficient therapy for severe and treatment-resistant depression, with rates and time to response surpassing other established treatments (3,4). However, despite its efficacy, the therapy remains controversial. This may be related to the poor understanding of its underlying neurobiological mechanisms and to reports of unwanted side effects. Identifying brain structural and functional correlates of clinical response is thus a major research goal, as it may help clarify the mechanisms of antidepressant action and also help identify patients that are most likely to benefit from ECT treatment.

Magnetic resonance imaging studies in patients receiving ECT have consistently reported increased volume of the

hippocampus (5–9) and surrounding structures (6,10–12), complementing reports of reduced hippocampal volume in depression (13). Moreover, animal models of ECT have shown a dose-related increase in hippocampal neurogenesis (14), which is a stem cell-containing niche in the adult human brain [(15); see (16)]. Together, these findings are taken in support of the neurogenic theory of depression, which postulates that depression hinders neurogenesis in the hippocampus (17,18) and that ECT may reverse this effect (12,14). However, apart from inducing neurogenesis, electroconvulsive seizures (ECS, the animal model of ECT) also stimulate gliogenesis, angiogenesis, and synaptogenesis (19–21), and these effects are not restricted to the medial temporal lobe. Furthermore, ECT-related changes in gray matter volume or density have been identified for numerous brain regions, including the basal

ganglia (22), temporal pole (23), insula (23), and anterior cingulate cortex (10,24,25).

Jointly these findings suggest more widespread effects of ECT than were initially proposed; however, the extent and distribution of changes vary considerably across studies. Moreover, although some studies report associations between volumetric changes and clinical response (10,12,24), these findings have generally not been replicated in meta- or mega-analyses (5,6,8). The inconsistencies may arise owing to variability in data acquisition and processing, in addition to clinical, treatment, and demographic heterogeneity. With regard to data processing, various techniques for assessing structural changes exist. Some studies use voxel-based morphometry to generate maps of gray matter density, whereas others use surface-based streams to generate maps of cortical thickness and surface area, or volume-based streams to generate maps of subcortical volumes. These techniques likely differ in their anatomical structure identification (26,27) and in their modeling of longitudinal changes. Moreover, the selective focus on a few regions of interest (ROIs), without taking the full brain into account, gives a fragmented understanding of the neurobiological effects of ECT.

To overcome some of these shortcomings, we established the Global ECT-MRI Research Collaboration (GEMRIC) (28), which aims to identify consistent brain alterations associated with ECT treatment in depression. The goal of the present study was to delineate whole-brain volumetric changes following ECT using the GEMRIC database and to extend our previous investigation of hippocampal volumetric changes following ECT (5). By performing a mega-analysis of single subject data, we tested whether whole-brain structural changes are associated with ECT treatment number, mode of electrode placement, and clinical outcome.

## METHODS AND MATERIALS

### Study Sample

Clinical and demographic characteristics of the total sample are detailed in Table 1. For information regarding each site's demographic and clinical characteristics, see Supplemental Figure S1 and Supplemental Table S6. In the present study, data from 14 sites were included, totaling 328 patients (60.7% female, mean age  $\pm$  SD: 54.6  $\pm$  16.3 years) and 95 control subjects (60.0% female, mean age  $\pm$  SD: 46.9  $\pm$  14.6 years). Patients were scanned before (within 1 week before the first ECT session) and after treatment completion (typically within 1 to 2 weeks after the final ECT session of the index series), except for site number 11, which scanned patients before and after the completion of 9 ECT sessions. Control subjects were similarly scanned at 2 time points. Depressive symptoms were rated by the Montgomery-Åsberg Depression Rating Scale (MADRS). For sites that had used the Hamilton Depression Rating Scale, a validated equation was used to convert the 17-item Hamilton Depression Rating Scale to MADRS (29). Owing to some missing data points, the final patient sample size used for the main statistical tests varied between 282 and 322 patients. ECT practice differed across sites in terms of electrode placement (right unilateral [RUL], bifrontal, and bitemporal), ECT charge, and pulse width [see (28)]. Moreover, most sites continued psychotropic medications during the ECT series.

**Table 1. Clinical and Demographic Characteristics of the GEMRIC Sample**

Subject Characteristics	Mean	SD	<i>n</i> <sup>a</sup>
<b>Patients</b>			
Age, years	54.6	16.3	328
Baseline cortical GM, cm <sup>3</sup>	519.7	63.2	300 <sup>b</sup>
Changes cortical GM, %	1.0	1.0	299
Baseline subcortical GM, cm <sup>3</sup>	52.5	6.0	300
Changes subcortical GM, %	1.5	1.1	295
Baseline WM, cm <sup>3</sup>	464.6	62.1	300
Changes WM, %	−0.02	0.5	299
Baseline ventricle volumes, cm <sup>3</sup>	30.7	18.5	300
Changes ventricle volumes, %	−4.9	6.7	299
Baseline intracranial volume, cm <sup>3</sup>	1489.0	189.0	300
Baseline depression score	34.0	8.3	324
Posttreatment depression score	14.4	10.9	322
Duration of episode, months	17.6	29.3	205
Number of ECTs, total	11.7	5.0	320 <sup>c</sup>
Bilateral only	12.6	6.5	89
Right unilateral only	10.6	3.6	186
Number of ECTs, responders	11.2	5.0	199
Number of ECTs, nonresponders	12.9	4.7	113
<b>Control Subjects</b>			
Age, years	46.9	14.6	95
Baseline cortical GM, cm <sup>3</sup>	556.4	56.9	95
Changes cortical GM, %	−0.1	0.5	95
Baseline subcortical GM, cm <sup>3</sup>	55.2	5.4	95
Changes subcortical GM, %	−0.06	0.4	95
Baseline WM, mm <sup>3</sup>	471.5	56.8	95
Changes WM, %	0.01	0.3	95
Baseline ventricle volumes, cm <sup>3</sup>	21.7	13.3	95
Changes ventricle volumes, %	0.05	3.9	95
Baseline intracranial volume, cm <sup>3</sup>	1520.1	179.2	95

ECT, electroconvulsive therapy; GEMRIC, Global ECT-MRI Research Collaboration; GM, gray matter; WM, white matter.

<sup>a</sup>Due to missing data for some variables, the number of subjects varies.

<sup>b</sup>Twenty-eight subjects were missing magnetic resonance imaging before or after treatment and were therefore excluded from all analyses.

<sup>c</sup>Information regarding number of ECTs was missing for 8 subjects. Of note, some subjects received  $\geq 1$  mode of electrode placement and 1 subject also received left anterior right temporal stimulation.

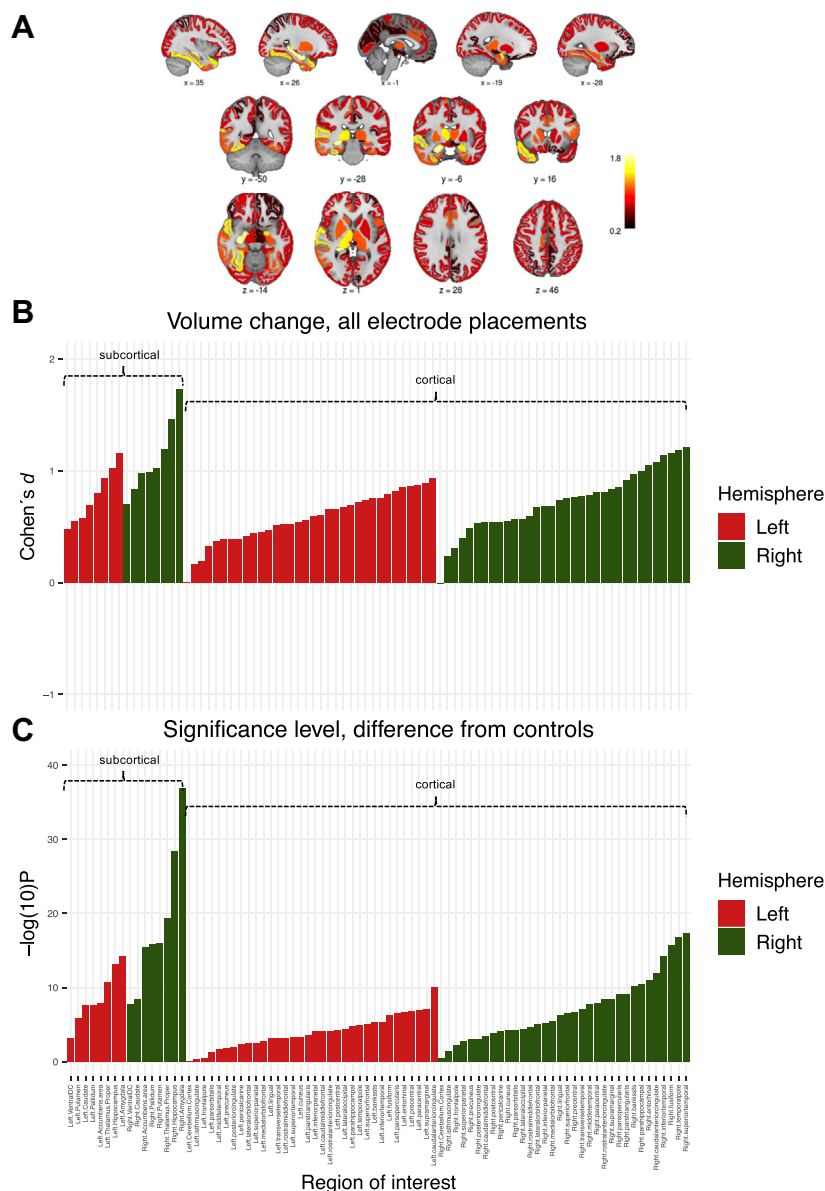
Medication information for each site is provided in Supplemental Table S1. All contributing sites received ethics approval from their local ethics committee or institutional review board. In addition, the centralized mega-analysis was approved by the Regional Ethics Committee South-East in Norway (No. 2013/1032).

### Image Acquisition and Postprocessing

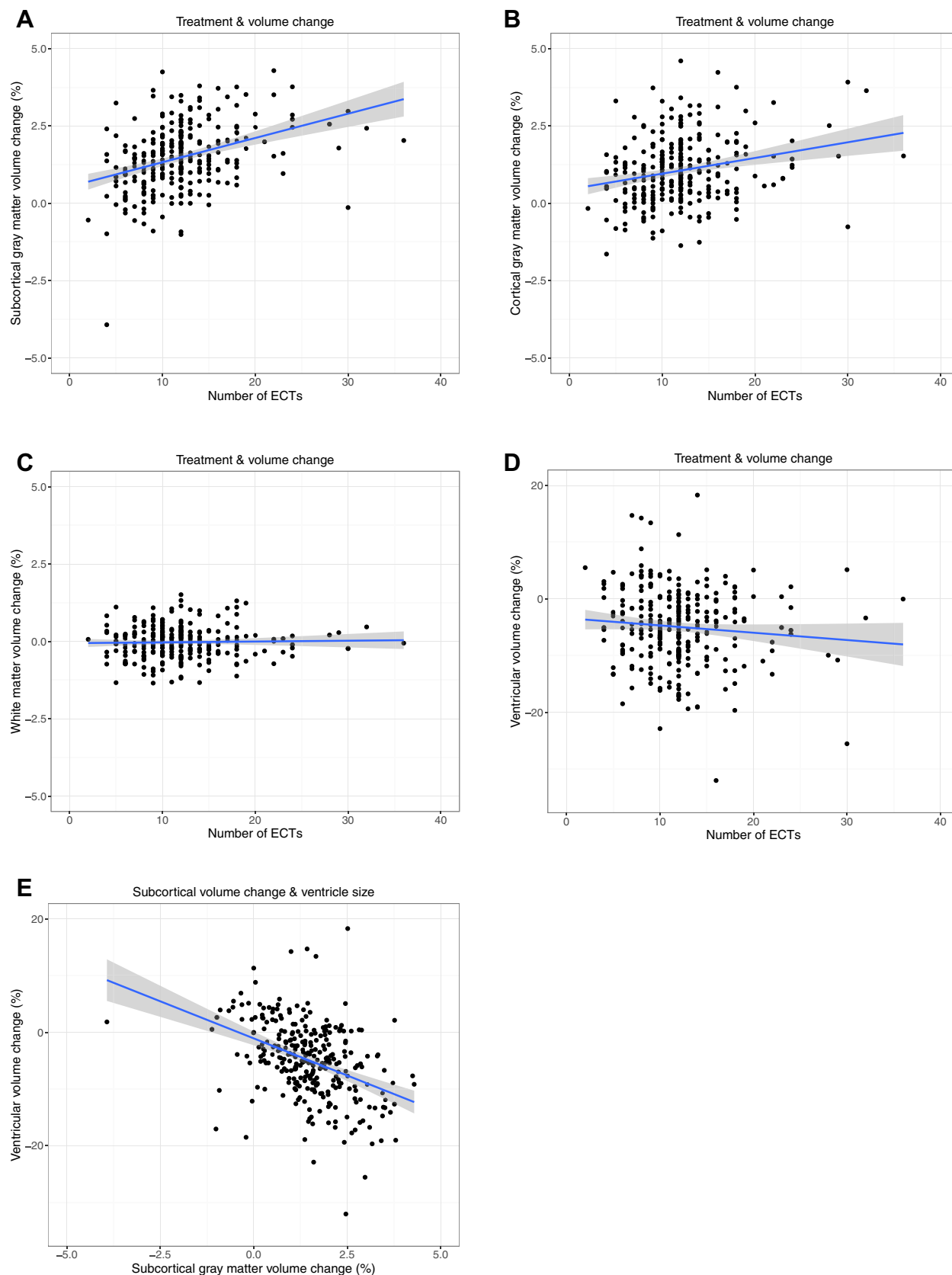
The image processing pipeline has been detailed elsewhere (5,28). In brief, 3-dimensional T1-weighted structural images with a minimum resolution of 1.3 mm in any direction were acquired at both time points using 1.5T (1 site) or 3T (13 sites) scanners (see Supplemental Table S6). Image processing and

analysis were performed by a pipeline optimized to increase the statistical power of detecting longitudinal cortical and subcortical anatomical change. Raw DICOM (Digital Imaging and Communication in Medicine) images as well as clinical and demographic information for individual patients and control subjects were transferred to a centralized data portal (30) for common analyses. Images were corrected for distortions caused by scanner-specific nonlinear gradient warp (31) and registered to a common atlas space and resampled to an isotropic 1-mm<sup>3</sup> spatial resolution. Cortical and subcortical segmentations were performed by FreeSurfer, version 5.3 (<https://surfer.nmr.mgh.harvard.edu/>) and included parcellation

of 66 (33 left and 33 right) cortical gray matter ROIs [based on the Desikan-Killiany atlas (32)] in addition to the 2 (left and right) cerebellar cortical gray matter and 16 (8 left and 8 right) default FreeSurfer subcortical gray matter regions. Next, Quarc (33,34) was used for unbiased estimation of volume change from pre- to posttreatment in all ROIs. In addition to the volume change of each separate region, the total volume changes of 4 main tissue compartments (ROI<sub>tc</sub>)—cortical gray matter, subcortical gray matter, white matter, and total ventricle volume—were estimated. We used the total ventricle volume from FreeSurfer, which consists of right and left lateral, third and fourth ventricles, to estimate the volumetric changes of the



**Figure 1.** Whole-brain volumetric changes following electroconvulsive therapy. **(A)** Graphical illustration of volumetric changes mapped to the brain. The colors refer to Cohen's *d* effect sizes as coded in the bar to the right of the images. Effect sizes for white matter and ventricles are not shown. **(B)** Cohen's *d* effect sizes for the volumetric changes of all cortical and subcortical gray matter regions of interest in patients (84 in total). All electrode placements were treated equally. **(C)** Group (i.e., patients vs. controls) differences in volumetric changes of the gray matter regions of interest. The model controlled for age, sex, site, and the respective baseline volumes. DC, diencephalon.



ventricles. For the remaining 3 tissue compartments, volumetric changes were calculated using weighted means:

$$ROI_{tc} = \frac{\sum_{i=1}^n (vol_{baseline} \times vol_{change})_i}{\sum_{i=1}^n vol_{baseline_i}}$$

where  $n$  was the number of ROIs included in the given  $ROI_{tc}$ , and  $vol_{baseline}$  and  $vol_{change}$  were the baseline volume and volume change for the  $i$ th ROI. The  $ROI_{tc}$  for 1) cortical gray matter consisted of left and right cortical and cerebellar gray matter volume, while the  $ROI_{tc}$  for 2) subcortical gray matter included the volumes of left and right thalamus proper, caudate, putamen, pallidum, hippocampus, amygdala, nucleus accumbens, and ventral diencephalon. Finally, the  $ROI_{tc}$  for 3) total white matter included the volumes of left and right subcortical and left and right cerebellar white matter. The quality of the whole-brain segmentation was ensured by using procedures adapted from the ENIGMA (Enhancing Neuro Imaging Genetics Through Meta Analysis) Consortium (<http://enigma.usc.edu/>) (35). Further details on the quality control procedure can be found in the [Supplement](#).

### Statistical Analyses

Statistical analysis was performed with the R software package, version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria) (36). Slopes of linear models are reported with mean  $\pm$  SE, while all other results are reported as mean  $\pm$  SD. Our first goal was to investigate the distribution of structural brain changes following ECT. Thus, we examined group differences in volumetric change scores for the 4 major tissue compartments (cortical or subcortical gray matter, white matter, or the ventricles) using general linear models. A binary indicator of diagnosis (patients vs. control subjects) was the predictor of interest. In addition, all models were controlled for age, sex, site, and the respective baseline volumes. To further delineate the anatomical distribution of the gray matter changes, we investigated each of the 84 gray matter ROIs (33 left and 33 right cortical, 8 left and 8 right subcortical, left and right cerebellum gray matter) separately using the same statistical framework detailed above. Because some sites did not provide data for healthy control subjects, we also investigated volumetric changes of all 84 ROIs and the 4  $ROI_{tc}$ s in patients and healthy control subjects separately, and the results of these analyses are provided in the [Supplement](#). Effect size estimates are reported as Cohen's  $d$  metric, calculated as  $dv/SD$  where  $dv$  represents the mean change estimate and  $SD$  the standard deviation for each anatomical ROI or tissue compartment. Throughout this article, we report false discovery rate (FDR)-corrected  $p$  values ( $p_{FDR} < .05$ ).

To address whether the number of ECT sessions influenced the volumetric changes, we performed separate general linear

models using the volumetric change of the 4 main tissue compartments as the outcome values and the number of ECTs as the predictor of interest. Number of ECT sessions was weighted similarly regardless of electrode placement across the sites. The analyses controlled for age, sex, site, the respective baseline volumes, and baseline depression scores. To control for nonlinear effects of ECT, we also included the number of ECT sessions squared as a covariate.

To examine the effect of electrode placement, we split the patients into subjects receiving RUL ( $n = 186$ ) versus bilateral ([BL];  $n = 89$ , of which 20 were bifrontal and 69 were bitemporal) stimulation only and tested for group differences in the left or right hemispheric cortical and subcortical gray matter changes using two-sample  $t$  tests. Patients switching mode of electrode placement during the course of treatment were excluded. We also investigated whether number of BL versus RUL ECTs affected the left hemispheric changes, by fitting separate linear models for the left cortical and subcortical gray matter  $ROI_{tc}$  and subsequently testing the difference in slopes between RUL and BL using the function Linear Hypothesis in R (car-package, version 2.1–6). The analyses controlled for age, sex, site, baseline depression score, and the respective baseline volumes. Finally, we examined the association between treatment response and the gray matter changes. In separate general linear models, we tested the association between clinical response (changes in MADRS pre–post ECT) and volumetric change of each gray matter ROI (i.e., the 84 anatomical ROIs and the 2 gray matter  $ROI_{tc}$ s) while controlling for age, sex, site, baseline depression score, number of ECTs, number of ECTs squared, and the respective baseline volumes.

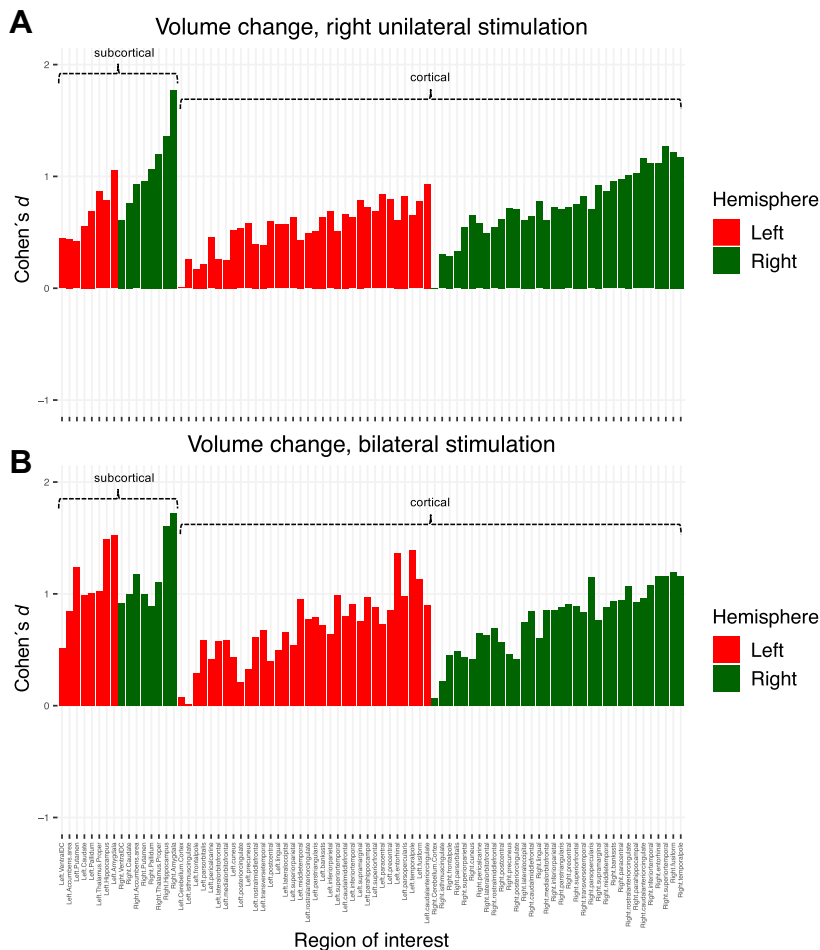
### RESULTS

The mean depression rating (MADRS score) of patients decreased from  $34.0 \pm 8.3$  at baseline to  $14.4 \pm 10.9$  after treatment ( $t_{319} = 27.24$ ,  $p < .001$ ). Moreover, 63.1% of the patients were classified as responders (>50% symptom reduction) and 46.6% of the patients were categorized as remitters (MADRS of <10 following the index series). Clinical and demographic characteristics of the responders and the remitters are detailed in the [Supplemental Results](#).

In our primary analyses, we assessed group differences in volumetric changes across 4 major tissue compartments while controlling for age, sex, site, and the respective baseline volumes. The analyses revealed significant volumetric enlargements of the cortical ( $t_{376} = 7.40$ ,  $p_{FDR} < .001$ ,  $d$  for patients = 1.01) and the subcortical ( $t_{372} = 11.70$ ,  $p_{FDR} < .001$ ,  $d = 1.40$ ) gray matter compartments in patients following ECT. Correspondingly, ventricle size decreased in patients over the course of the ECT index series ( $t_{376} = -5.09$ ,  $p_{FDR} < .001$ ,  $d = -0.74$ ), while no significant changes emerged for the white

**Figure 2.** Differential effect of electroconvulsive therapy (ECT) on 4 major tissue compartments. **(A)** Scatter plot of the association between volumetric changes of subcortical gray matter and number of ECTs. Subcortical gray matter included the volumes of left and right thalamus proper, caudate, putamen, pallidum, hippocampus, amygdala, nucleus accumbens, and ventral diencephalon. **(B)** Scatter plot of the association between volumetric changes of cortical gray matter and number of ECTs. Cortical gray matter consisted of left and right cortical and cerebellar gray matter. **(C)** Scatter plot of the association between volumetric changes of total white matter and number of ECTs. Total white matter included the volumes of left and right subcortical and left and right cerebellar white matter. **(D)** Scatter plot of the association between the changes of total ventricle volume and number of ECTs. Total ventricle volume consisted of right and left lateral, third and fourth ventricles. **(E)** Scatter plot of the association between ventricular and subcortical volumetric changes.





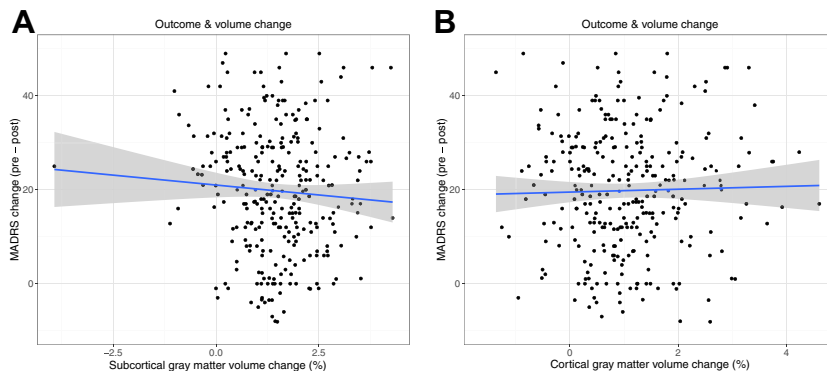
**Figure 3.** Whole-brain volumetric changes following electroconvulsive therapy based on electrode placement. **(A)** Cohen's *d* effect sizes for the volumetric changes of all cortical and subcortical gray matter regions of interest in patients receiving right unilateral stimulation. **(B)** Cohen's *d* effect sizes for the volumetric changes of all cortical and subcortical gray matter regions of interest in patients receiving bilateral stimulation. Bilateral stimulation included bifrontal and bitemporal electrode placement. DC, diencephalon.

matter compartment ( $t_{376} = -0.05$ ,  $p_{FDR} = .96$ ,  $d = -0.05$ ). The volumetric changes were broadly distributed across cortical and subcortical gray matter ROIs, with effect sizes ranging between 0.009 and 1.73 (Figure 1A, B), and the volume change was statistically significant for 79 of the 84 gray matter ROIs (Figure 1C, Supplemental Table S2). A within-group comparison of volumetric changes in patients revealed significant volumetric alterations in all ROIs except for the white matter ROI<sub>tc</sub> and cerebellar gray matter (Supplemental Table S3). No changes were observed in control subjects (Supplemental Table S4).

We next investigated how number of ECTs may relate to the volumetric changes of the 4 tissue compartments while controlling for age, sex, site, the respective baseline volumes, baseline depression scores, and number of ECTs squared. Volumetric increase as a function of number of ECTs was found for both subcortical (slope  $0.21 \pm 0.04$ ,  $t_{263} = 5.15$ ,  $p_{FDR} < .001$ ) (Figure 2A) and cortical (slope  $0.12 \pm 0.04$ ,  $t_{267} = 3.05$ ,  $p_{FDR} = .006$ ) (Figure 2B) gray matter, while there was no association for white matter (slope  $0.006 \pm 0.02$ ,  $t_{267} = 0.28$ ,  $p_{FDR} = .78$ ) (Figure 2C). Moreover, the number of ECTs-squared term was significant for subcortical volume changes

( $t_{263} = -3.49$ ,  $p_{FDR} = .002$ ), suggesting significant volumetric changes also in subjects receiving shorter ECT series. Corresponding to the increase in gray matter volume, and in accord with the Monroe-Kellie doctrine (37), ventricle volume was negatively associated with number of ECT sessions (slope  $-0.69 \pm 0.29$ ,  $t_{267} = -2.34$ ,  $p_{FDR} = .03$ ) (Figure 2D). Moreover, there was a negative association between changes in subcortical gray matter and ventricle volumes; thus, patients experiencing the greatest subcortical volumetric increase also had the largest ventricle volume reductions (Spearman's rank correlation  $\rho = -.44$ ,  $p < .001$ ) (Figure 2E). The magnitude of change for subcortical, cortical, white matter, and ventricle volume across sites are shown in Supplemental Figure S2. Finally, adding psychotropic medication as an additional covariate in the models did not influence the results (see Supplemental Results).

While all subjects received right hemisphere stimulation (RUL, bifrontal, bitemporal), only a subsample also received stimulation of the left hemisphere (bitemporal or bifrontal). Accordingly, the distribution of effect sizes of volume change per gray matter ROI differed for patients receiving RUL-only versus BL-only stimulation (Figure 3A, B). A comparison of



**Figure 4.** The association between brain volumetric effects and clinical response. **(A)** Scatter plot of the association between subcortical gray matter volumetric changes and changes (pre-post electroconvulsive therapy index series) in Montgomery-Åsberg Depression Rating Scale (MADRS). Subcortical gray matter included the volumes of left and right thalamus proper, caudate, putamen, pallidum, hippocampus, amygdala, nucleus accumbens, and ventral diencephalon. **(B)** Scatter plot of the association between cortical gray matter volumetric changes and changes in MADRS. Cortical gray matter consisted of left and right cortical and cerebellar gray matter.

electrode placement for the left subcortical ROI<sub>tc</sub> revealed greater volumetric enlargements for BL with respect to RUL stimulation ( $t_{152} = 3.70$ ,  $p_{FDR} = .002$ , two-sample  $t$  test). An equivalent analysis for left cortical ROI<sub>tc</sub> was not significant ( $t_{125} = 2.06$ ,  $p_{FDR} = .12$ ). Changes in right subcortical ( $t_{152} = 0.14$ ,  $p_{FDR} = .89$ ) or cortical ( $t_{138} = 0.15$ ,  $p_{FDR} = .89$ ) ROI<sub>tc</sub>s did not differ for BL versus RUL electrode placement. We also investigated whether mode of electrode placement differently affected the left hemisphere's gray matter expansion per ECT session, by constructing separate linear models for the left cortical and subcortical tissue compartments, and subsequently comparing the slopes for the number of RUL versus BL ECT sessions. The slopes of left cortical ROI<sub>tc</sub> ( $0.06 \pm 0.02$  vs.  $0.06 \pm 0.02$ ) and subcortical ROI<sub>tc</sub> ( $0.05 \pm 0.02$  vs.  $0.07 \pm 0.02$ ) volume change per ECT session did not differ for RUL versus BL electrode placements, respectively. This was further confirmed by comparisons of the slopes in a linear hypothesis test (subcortical  $p = .49$ , cortical  $p = .99$ ). Also, change in MADRS score per ECT session did not differ between RUL and BL stimulation (Supplemental Results, Supplemental Figure S3).

Finally, we analyzed the relationship between the gray matter volumetric changes and treatment outcome, measured using the MADRS. We tested all anatomical gray matter ROIs in addition to the weighted means of cortical and subcortical gray matter change. There were no significant associations between changes in subcortical (slope =  $-1.06 \pm 0.66$ ,  $t_{262} = -1.60$ ,  $p_{FDR} = .22$ ) (Figure 4A) or cortical (slope =  $-0.56 \pm 0.64$ ,  $t_{266} = -0.88$ ,  $p_{FDR} = .38$ ) (Figure 4B) gray matter volumes and clinical improvement following the index series. Furthermore, although nominal significant associations emerged between the volumetric changes of right rostral middle frontal ( $t_{266} = -2.80$ ,  $p = .006$ ), right putamen ( $t_{266} = -2.00$ ,  $p < .05$ ), left accumbens ( $t_{266} = -2.33$ ,  $p = .02$ ), and clinical response (Supplemental Table S5), none of these survived correction for multiple comparisons. In addition to testing each ROI separately for an association with clinical response, we also conducted a multiple linear regression of clinical response against all anatomical ROIs simultaneously. The results of this analysis can be found in the Supplemental Results. Finally, there were no differences in gray matter changes between responders and nonresponders or between remitters and nonremitters (Supplemental Results, Supplemental Figure S4).

## DISCUSSION

We here report that the structural changes following ECT in depression are broadly distributed. Using the largest sample size to date, we observed volumetric increases in widespread cortical and subcortical gray matter areas that varied based on the number of ECTs and mode of electrode placement. The subcortical gray matter changes were inversely associated with changes in ventricle volumes, while white matter volume remained unchanged. Finally, the volume enlargements of cortical and subcortical gray matter regions did not significantly relate to treatment outcome. Thus, our results indicate that gross volumetric increases of specific cortical or subcortical regions may not serve as viable biomarkers of clinical response.

As in our previous study, the gray matter volumetric effects were strongly related to number of ECTs and mode of electrode placement (5). Thus, volumetric changes of a broad set of brain regions beyond the hippocampus scaled positively with the number of ECTs. Although the gray matter expansion was general, the effects predominated in regions closest to the temporal electrodes, which are subjected to the highest electrical stimulation. Moreover, the subcortical volumetric changes varied based on electrode placement, and thus, compared with BL electrode placement, RUL led to more right lateralized effects (38). This fits with computational modeling of electrical fields demonstrating more diffuse brain stimulation with BL than with RUL (39,40) and suggests that the neurotrophic response to ECT is not related only to its capacity to generate generalized seizure activity. Indeed, preclinical models have demonstrated a dose-dependent association between stimulus charge and dendritic arborization (41), implying that the electric field impacts ECT-related neuroplastic processes. However, although the regional distribution of the subcortical volumetric changes varied based on mode of electrode placement, it was independent of number of RUL versus BL ECT sessions. Accordingly, the relationship between ECT electric field distribution and whole-brain changes in gray and white matter warrants further investigations.

While the majority of studies investigating the neurobiological underpinnings of ECT have reported that ECT alters specific brain regions or neural networks, we found widespread volumetric increases encompassing most cortical and subcortical gray matter regions. Moreover, the subcortical

volumetric enlargements were negatively associated with ventricle volumes, which accords with the Monro-Kellie doctrine stating that the sum of volumes of intracranial compartments is constant (37). A number of neurophysiological, immunological, and neurotrophic processes may contribute to the gray matter volumetric expansions, and these may not necessarily coincide with the ECT therapeutic effects. Neurotrophic factors supporting the growth and maintenance of neurons are upregulated in plasma of ECT-treated patients (42,43). In concert, preclinical studies have demonstrated increased levels of neurotrophic factors including brain-derived neurotrophic factor in the hippocampus and the prefrontal cortex following ECS (44), potentially resulting in an absolute increase in number of cells, dendrites, or synapses, which may be detected by T1 magnetic resonance imaging sequences (45,46). In addition to the neural effects, ECS also induces proliferation (21) and activation (47) of glial cells in other limbic and paralimbic brain regions, and the glial cell proliferation has been linked to hippocampal volumetric increases (20). Alternatively, volume expansion may be ascribed to changes in extracellular fluid, in either the vascular or the extravascular compartments. Neurotrophic processes are inevitably linked to vascular changes (48,49), and thus most neurotrophic factors also possess some angiogenic properties. This finding is further substantiated by studies reporting focal and global changes in brain perfusion (50,51) following ECT, and the regional distribution of these changes corresponds to those observed in brain volumetric studies. Finally, inflammatory mechanisms may be associated with, or be a mediator of, the various trophic and vascular effects (10,52).

The amygdala and hippocampus showed the largest effect sizes in the present study, which accords with pathophysiological models of depression positing dysfunctional limbic circuits as a core mechanism of these disorders (13,53). In addition, the findings coincide with meta- and mega-analyses of structural changes following ECT, reporting robust volumetric expansions of hippocampus and the amygdala (5,6), potentially as a result of neurogenesis in the hippocampus (14,54,55). However, consistent with our previous results, the ECT-related volumetric changes of these brain regions did not predict clinical response (5). Of note, animal models suggest specificity of the neuroplastic effects, with neurogenesis occurring in the dentate gyrus of the hippocampus (14) and attenuated dendritic arborization in the basolateral complex of the amygdala (56). Furthermore, the expression of voltage-gated calcium channels in the basolateral complex and the dentate gyrus are selectively downregulated by ECS (57), which is likely to improve neuronal survival (58). As such, studies of global volumetric changes of these brain areas may not be sensitive to ECT outcome, which is appreciated by recent studies further dividing these brain areas into their respective subfields. The results of these preliminary studies indicate differential effects of ECT on hippocampal subfields or amygdala nuclei (59–61), and the volumetric changes of the dentate gyrus may be indicative of the clinical response (61).

Our finding of large and relatively comparable volumetric treatment effects in numerous brain regions suggests a rather unspecific effect of ECT; thus, an association with clinical response may appear unlikely. Although associations between the volumetric changes of certain striatal and prefrontal brain

regions and clinical response were found at an uncorrected significance level, none of these survived correction for multiple comparisons. Accordingly, we could speculate that measures of large-scale volumetric changes of the brain may not relate to the therapeutic effects of ECT. Alternatively, the structural changes induced by ECT may precede or lag behind clinical response, or the effects of seizure therapy on brain volumes may mask subtle effects related to treatment outcome. ECT may modulate the differentiation and function of serotonergic neurons through its effect on brain-derived neurotrophic factor levels (42,62). Furthermore, ECT leads to a global decrease in postsynaptic serotonin 1A receptor binding (63), similar to standard antidepressant treatment (64). Despite co-occurring neuroplastic and molecular effects, only the molecular effects may be a key mechanism underlying the therapeutic success of ECT. Thus, if successful ECT treatment depends on rearrangement of neuronal networks on a molecular level, this will most likely not be captured by investigations of whole-brain volumetric effects.

We did not observe significant whole-brain changes in white matter volume. This may at first seem contradictory, as previous studies have reported altered structural and functional brain connectivity ascribed to white matter changes (65,66). However, the majority of studies have investigated the diffusion properties of (specific) white matter tracts, while we report on the whole-brain white matter volume. Finally, it is possible that white matter changes lag behind gray matter increase, and thus our follow-up time may not have been sufficient to discover such changes.

One limitation of the present study rests in the heterogeneity of the patient sample. Although we explicitly modeled differences between sites and ran all raw data through the same processing pipeline, sources of heterogeneity are likely to remain. However, heterogeneity allows greater generalizability and translational value, as indeed the patients' eligible for ECT varies across the globe. A second limitation is that the RUL versus BL electrode placements were not counterbalanced, and thus any patient characteristic leading to the preference of electrode placement was also not controlled for. A third limitation is that not all sites included healthy control subjects. To avoid potential biases introduced by the control sample, we therefore used 2 independent analyses when testing for volumetric changes in patients. Finally, we note that previous studies investigating cortical gray matter changes following ECT have mainly used cortical thickness and not cortical volume. However, volume change is the only parameter that can be applied to all tissue compartments (i.e., cortical gray matter, subcortical gray matter, white matter, and cerebrospinal fluid spaces), which permits a full assessment of brain structural changes following ECT.

In conclusion, we found that ECT induces volumetric enlargements of widespread cortical and subcortical gray matter regions, supporting the assumption that ECT induces trophic processes in brain gray matter. The subcortical gray matter expansion scaled negatively with ventricle size, while white matter volume remained unchanged; thus, the sum of volumes of intracranial compartments remained unchanged. Although measurements of gross volumetric enlargements were not related to ECT clinical response, future studies should investigate whether microstructural or molecular changes related to



brain gray matter could explain clinical outcome. Delineating the macroscopic brain changes following ECT is an important step toward understanding ECT's mechanisms of action, ultimately leading to more effective personalized treatment approaches for depressive disorders.

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LO wrote the first draft and coordinated the work. OTO analyzed and interpreted the data in collaboration with LO, AMD, KLN, and MA. OTO also wrote the final manuscript draft. LO, UK, HB, KJO, OBP, CA, and AMD contributed in planning and/or design of the project. All authors contributed data, as well as critical revision of the manuscript. All authors approved the final manuscript.

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